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Gina N. Shishima

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Xiang et al.

Serial No.: 09/828,498

Filed: April 5, 2001

For: FULL-LENGTH GB VIRUS C (HEPATITIS G VIRUS) RNA TRANSCRIPTS ARE INFECTIOUS IN PRIMARY CD4 POSITIVE T CELLS AND METHODS OF TREATING HIV

Group Art Unit: 1648

Examiner: Winkler, Ulrike

Atty. Dkt. No.: IOWA:030US

DECLARATION OF JACK T. STAPLETON, M.D.

I, Jack T. Stapleton declare:

1. I am one of the inventors on the above-referenced patent application.

2. I am a citizen of the United States. I reside at 602 Clark St., Iowa City, Iowa 52240.

3. I am a Professor at the University of Iowa in the Department of Internal Medicine. I am also the Director of the University of Iowa HIV Program and the Director of the Helen C. Levitt Center for Viral Pathogenesis and Disease. I am a staff physician at Iowa City V.A. Medical Center. I have been conducting research in the area of infectious diseases, including hepatitis viruses such as GVB-C, for more than19 years.

4. I understand that the claims in the above-referenced patent application have been rejected in the most recent Office Action as lacking novelty based on a number of references.

These references include Kim *et al.*, U.S. Patent 5,856,134 ("Kim"); Xiang *et al.*, *J. Virol.* 72:2738-2744, 1998 ("Xiang"); and, Pilot-Matias *et al.*, U.S. Patent 6,156,495 ("Pilot-Matias").

5. I have reviewed the Kim reference and am familiar with this work. This reference does not teach nor describe an "isolated and purified nucleic acid molecule encoding an infectious GBV-C," as recited by the claims in the patent application. In the Examples provided in Kim, they show only that clones with segments of HGV sequence are isolated, but these clones were never tested for infectivity. In Example 5, the authors show that they isolated viral particles from the serum of a patient (PNF2161). The RNA was extracted from these particles, but was never tested for infectivity. Furthermore, because the serum from PNF2161 was never tested for infectivity, one could not know whether the extracted RNA might be infectious.

6. Moreover, I understand that the Office Action asserts that the Kim references discloses the entire coding region of two hepatitis G virus DNA clones, which are 9.4 kilobases in size, corresponding to SEQ ID NOs: 14 and 182. It also contends that the reference discloses the expression and purification of HGV virus protein using a GST fusion. However, neither of these examples shows the clones were "infectious." First, SEQ ID NOs: 14 and 182 do not represent the sequences of single clones. Instead, the authors generated a number of clones from serum PNF2161 that represented only portions of the HGV genome and sequenced these segment clones. The cumulative sequences of the each HGV clone is represented by SEQ ID NOs: 14 and 182. The segment clones were never put together as an intact, single molecule. Significantly, the authors never tested any clone, segment or otherwise, for infectivity in culture. As discussed in the previous

paragraph, the serum from which the clones were made was also not tested for infectivity. Thus, nothing in the Kim reference discloses what is claimed in our patent application.

7. I am a co-author of the Xiang reference. In that paper, we disclosed the isolation of HGV RNA molecules, but we never tested the infectivity of those RNA molecules. Furthermore, this reference says nothing about the sequence of an infectious GVB-C nucleic acid molecule.

8. I have reviewed the Pilot-Matias reference and am familiar with the work disclosed in it. It does not show the infectivity of any nucleic acids from a GVB-C, nor does it show that the serum from which GVB-C particles was isolated contains infectious virus. It provides no information regarding the infectivity of any nucleic acid molecules as claimed in the present application. Furthermore, the protein that the Pilot-Matias group expressed does not include replicative proteins necessary for replication. Accordingly, it would not replicate in a cell.

9. I hereby declare that all statements made of my own knowledge are true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

2/17/03
Date

Jack T. Stapleton, M.D.